

REMARKS**I. OVERVIEW**

Applicants have reviewed and considered the Office Action dated July 28, 2004, and the references cited therewith. Claims 1-26 are now pending in this application. Claims 7-26 are withdrawn from consideration. Applicants respectfully request reconsideration of the above-identified application in view of the amendments above and the remarks that follow.

II. CLAIM OBJECTIONS

A. Claims 1 and 3-6 were objected to because of the recitation of "CYP2E1." The Examiner states that abbreviations should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Accordingly, Applicants have amended claim 1 to recite "of (i) Cytochrome P4502E1 (CYP2E1)," and respectfully request that Examiner withdraw his objection.

B. Claims 1 and 3-6 were objected to because of the following informalities: the term is misspelled and should be replaced with, for example "sulfotransferase." Applicants thank Examiner for pointing out this misspelling and as a result have replaced the word "sulfotransfease" with "sulfotransferase." Applicants respectfully request that Examiner withdraw his objection.

C. The Examiner states that preamble of claim 1 states, "a method for determining the susceptibility of a male pig," while the body of the claim recites "the pig." In the interest of clarity, the Examiner suggests that the Applicants amend "the pig" in the body of claim 1 to "the male pig." Applicants thank Examiner for his suggestion and have adopted the recitation of "the

male pig in claim 1, replacing "the pig." Applicants respectfully request that Examiner withdraw his objection.

D. Claims 3-6 were objected to because of the following informalities: the term "indicate" appears to be grammatically incorrect and should be replaced with, for example "indicates." Applicants respectfully disagree and respectfully direct Examiner's attention to the subject of the verb "levels of CYP2E1 and/or ... sulfotransferase". Therefore, the subject "levels" requires the verb "indicate" to be grammatically correct. Applicants respectfully request that Examiner withdraw his objection.

III. CLAIMS REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

A. Claims 1-6 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that claim 1 (claims dependent therefrom) and 2-6 are indefinite in the recitation of "levels." This term is typically interpreted as an amount of a protein. However the specification discloses that the enzyme activity and not amount is related to a determination of developing boar taint. The Examiner states it is unclear whether the term is meant to be interpreted as an amount of an enzyme or an amount of an enzyme activity. The Examiner suggests that Applicants clarify the meaning of the claim. In the interest of advancing prosecution, the Examiner has interpreted the term according to its art-recognized definition as being an amount of a protein.

Applicants have amended claim 1 to recite "(b) detecting the enzymatic activity or protein levels of one or more enzymes". Applicants respectfully submit that the claim language

in question, when analyzed in light of the content of the application disclosure, is now definite.

The application disclosure, at page 6-7, tables 3-4 provides that

Levels of CYP2E1 can be measured using techniques known in the art including Western blotting as described in Example 1. Levels of CYP2E1 mRNA can also be measured by Northern analysis or quantitative PCR. Other methods include measuring the biological activity of the enzyme. For example, the activity of CYP2E1 can be measured by assaying its characteristic reactions, for example assaying for N-nitrosodimethylamine demethylase activity, aniline hydroxylase activity or p-nitrophenol hydroxylase activity as described in Xu et al., 1994. Alternatively, the activity of CYP2E1 can be measured by inhibiting the metabolism of skatole using known CYP2E1 inhibitors such as diallylsulfide and chlorozoxazone as described in Example 1, or 4-methylpyrazole as described in Halpert, et al." [emphasis added].

The application disclosure further discusses that levels of thermostabile phenol sulfotransferase and glucuronyl transferase may measured either by protein levels using Western blotting or measured by enzymatic activity using enzymatic assays on pages 7-9. Thus, Applicants respectfully request that the rejection be withdrawn and submit that amended claim 1 and dependent claims 2-6 are in condition for allowance.

B. The Examiner alleges that "high levels of CYP2E1," "high levels of a thermalstable phenol sulfotransferase," and "low levels of a glucuronyl transferase" in claim 1 (claims 2-6 dependent therefrom) are unclear absent a statement defining to what the levels of the respective enzyme is being compared. The Examiner states that the terms are relative terms and the claim should define and clearly state as to what the level of each enzyme is being compared. Applicants respectfully disagree regarding the indefiniteness of the quoted passage. The Board of Patent Appeals and Interferences has stated:

In rejecting a claim under the second paragraph of 35 U.S.C. § 112, it is incumbent on the examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims. *Ex parte Wu*, 10 USPQ 2d 2031, 2033 (B.P.A.I. 1989)

(citing *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (C.C.P.A. 1971); *In re Hammack*, 427 F.2d 1378, 166 USPQ 204 (C.C.P.A. 1970)).

The M.P.E.P. adopts this line of reasoning, stating that:

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (1) the content of the particular application disclosure; (2) the teachings of the prior art; and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *M.P.E.P.* § 2173.02.

Applicants respectfully submit that the claim language in question, when analyzed in light of the content of the application disclosure, is not unclear or indefinite. The application disclosure, at page 7, with respect to high levels of CYP2E1 provides that

[t]he term "*high levels of CYP2E1*" means that the sample contains the same or higher levels of CYP2E1 than in a suitable control. Suitable controls include female pigs and male pigs that are known to have boar taint. When the control is a female pig "*high levels of CYP2E1*" means levels in the test pig are the same or higher than the control pig. When the control pig is a pig with boar taint, "*high levels of CYP2E1*" means levels in the test pig are higher, preferably about 2-3 times higher than the level in a pig with boar taint. More preferably, the levels in the test pig are higher, preferably 2-3 times higher than the average level of CYP2E1 found in a group of pigs with boar taint. By "group" of pigs it is meant at least about 6 to about 10 male pigs. (emphasis added).

The application disclosure, at page 8, with respect to high levels of a thermostable phenol sulfotransferase provides that

[t]he term "*high levels of a thermostable phenol sulfotransferase*" means that the sample contains the same or higher levels of a thermostable phenol sulfotransferase than in a suitable control. Suitable controls include female pigs and male pigs that are known to have boar taint. When the control is a female pig, "*high levels of a thermostable phenol sulfotransferase*" means levels in the test pig are the same or higher than the control pig. When the control pig is a pig with boar taint, "*high levels of a thermostable phenol sulfotransferase*" means levels in the test pig are higher, preferably about 2 times higher, more preferably about 3-4 times higher than the level in a pig with boar taint, more preferably the levels in the test pig are higher, preferably about 2 times higher, more preferably about 3-4 times higher than the average level of thermostable phenol sulfotransferase found in a group of pigs with boar taint. By "group" of

pigs it is meant at least about 6 to about 10 male pigs. When expressed in terms of enzyme activity the term "high levels of a thermostable phenol sulfotransferase" preferably means that a sample has an enzyme activity of greater than about 0.3, preferably greater than about 0.5, wherein activity is expressed as nm of 5-sulfatoxyskatole per minute per mg of protein. (emphasis added).

The application disclosure, at page 9, with respect to low levels of glucuronyl transferase provides that

[t]he term "*low levels of glucuronyl transferase*" means that the sample contains the same or lower levels of glucuronyl transferase than in a suitable control. Suitable controls include female pigs and male pigs that are known to have boar taint. When the control is a female pig, "low levels of glucuronyl transferase" means levels in the test pig are the same or lower than the control pig. When the control pig is a pig with boar taint, "low levels of glucuronyl transferase" means levels in the test pig are lower, preferably about 50% lower than the level of glucuronyl transferase found in a male pig with boar taint, more preferably the levels in the test pig are lower, preferably about 50% lower than the average level of glucuronyl transferase in a group of male pigs with boar taint. By "group" of pigs it is meant at least about 6 to about 10 male pigs. (emphasis added).

In light of the definitions in the specification, Applicants respectfully submit that the rejection of claim 1 has been overcome, and that claim 1 and dependent claims 2-6 are in condition for allowance.

C. The Examiner alleges that claims 1 (claim 2 dependent therefrom) and 3-6 are indefinite in the recitation of "a thermostable phenol sulfotransferase" as it is unclear as to how heat stable a phenol sulfotransferase must be to be included within the scope of the claims.

Applicants respectfully disagree. The Board of Patent Appeals and Interferences has stated:

In rejecting a claim under the second paragraph of 35 U.S.C. §112, it is incumbent on the examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims. *Ex parte* Wu, 10 USPQ 2d 2031, 2033 (B.P.A.I. 1989) (citing *In re* Moore, 439 F.2d 1232, 169 USPQ 236 (C.C.P.A. 1971); *In re* Hammack, 427 F.2d 1378, 166 USPQ 204 (C.C.P.A. 1970)).

The M.P.E.P. adopts this line of reasoning, stating that:

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (1) the content of the particular application disclosure; (2) the teachings of the prior art; and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *M.P.E.P.* § 2173.02.

Applicants respectfully submit that the term "thermostabile phenol sulfotransferase" in question, when analyzed in light of the content of the application disclosure, is not unclear or indefinite. The application disclosure, at page 11, with respect to thermostabile phenol sulfotransferase provides that thermostabile and thermolabile phenol sulfotransferases "differ in their physical properties, substrate specificities, inhibitor sensitivities and regulation." The specification further discusses at numerous points, including pages 11 and 40, that thermostabile phenol sulfotransferase catalyzes the sulfate conjugation of micromolar levels of p-nitrophenol and other simple phenols and is sensitive to inhibition by 2,6-dichloro-4-nitrophenol (DCNP) and pentachlorophenol (PCP), whereas the thermolabile phenol sulfotransferase is active with micromolar levels of dopamine and other naturally occurring monoamines and is resistant to inhibition by DCNP and PCP. Thus, one of skill in the art would be able to distinguish between a thermolabile and a thermostabile phenol sulfotransferase solely based on physical properties, substrate specificities, or inhibitor sensitivities. Therefore, it is moot as to how heat stable a thermostabile phenol sulfotransferase must be to be included within the scope of the claims.

In light of the definitions in the specification, Applicants respectfully submit that the rejection of claim 1 has been overcome and that claim 1 is in condition for allowance. Similarly,

claims 2-6, dependent on definite claim 1, are likewise definite. Applicants respectfully submit that claims 1-6 are in condition for allowance.

D. The Examiner states that claims 2-6 are indefinite in the recitation of "[a] method" and it is suggested that these claims be amended to recite the definite article "the method." Applicants thank Examiner for pointing out the incorrect antecedent basis and consequently have replaced the word "[a] method" with "the method." Applicants respectfully submit that the rejection of claims 2-6 have been overcome, request withdrawal of the rejection and assert that claims 2-6 are in condition for allowance.

E. The Examiner states that claims 3-4 are confusing in the recitation of "the pig has a reduced susceptibility" as it is unclear as to whether "the pig" refers to a female control pig (claim 3) or a male control pig (claim 4) or whether "the pig" refers to the male pig whose susceptibility for developing boar taint is being determined.

Applicants thank Examiner for his suggestion and have amended claims 3 and 4 so that they now recite "the male pig has a reduced susceptibility to developing boar taint", replacing "the pig has a reduced susceptibility to developing boar taint." In light of the amendment, Applicants believe they have overcome Examiner's rejection and request reconsideration of claims 3 and 4.

IV. CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner states that the claims are drawn (in relevant part) to a method for determining the susceptibility of a male pig to developing boar taint by measuring the levels of a genus of thermostable phenol sulfotransferases and a genus of glucuronyl transferases. The Examiner then cites § 2163 of the MPEP stating that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus. The Examiner states that a representative number of species means that the species that are adequately described are representative of the entire genus. The Examiner then states that when there is a substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The Examiner states that in this case the specification discloses only a single representative species of the genus of recited thermostable phenol sulfotransferase, i.e., sulfotransferase that sulfates 2-naphthol, and only a single representative species of the genus of recited glucuronyl transferases, i.e., a glucuronyl transferase that glucuronidates para-nitrophenol and 2-naphthol. The Examiner then states that the specification fails to describe any additional representative species of the recited genera of enzymes. The Examiner states that in the instant case the recited genus of thermostable phenol sulfotransferases and glucuronyl transferases encompasses species that are widely variant. The Examiner then states as such, the disclosure of the single representative species of thermostable phenol sulfotransferases and glucuronyl transferases is insufficient to be representative of the attributes and features of all species encompassed by the

recited genus of thermostable phenol sulfotransferases and glucuronyl transferases. The Examiner states that given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that the applicant was in possession of the claimed invention. Applicants traverse this rejection for the following reasons.

Applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art". *Regents of University of California v. Eli Lilly*, 119 F.3d 1559, 1569 (Fed. Cir. 1997). This issue is further addressed in the USPTO's Written Description Guidelines:

A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the member of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. *Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. (emphasis added)*

It is thus not necessary that the specification describe each individual species embraced by a genus claim. Instead, whether an adequate description has been made of a genus claim is determined by whether or not a sufficient variety of species has been described to reflect variation within the genus and whether one skilled in the art would recognize that the Applicant was in possession of the "common attributes or features of the elements possessed by the member of the genus in view of the species disclosed." See, e.g., *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

The written description requirement may be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, *other physical and/or chemical properties*, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). (emphasis added).

Applicants' invention relates to a method for determining the susceptibility of a male pig to developing boar taint based on the association between the levels of skatole in a pig compared with the levels of one or more enzymes selected from CYP2E1; a thermostable phenol sulfotransferases and glucuronyl transferases that play important roles in skatole metabolism.

The specification describes sulfotransferases and glucuronyl transferases with specific chemical properties and common attributes. Specification, at page 11. The Applicants at the bottom of page 11 disclose that the "thermostable form of PST (TS-PST) catalyzes the sulfate conjugation of micromolar levels of p-nitrophenol and other simple phenols and is sensitive to inhibition by 2,6-dichloro-4-nitrophenol (DCNP) and pentachlorophenol (PCP). (Herndndez et al., 1991; Rein et al., 1982)." The specification further states that "p-nitrophenol is the model substrate for the measurement of TS-PST activity (Weinshilboum, 1990)." Therefore, Applicants have provided several properties by which to identify a thermostabile phenol sulfotransferase. First, the thermostabile phenol sulfotransferase catalyzes the O-sulfation of simple phenolic compounds, including p-nitrophenol and other simple phenols. Specification, at pages 8, 11, 40. Second, the thermostabile phenol sulfotransferase is sensitive to inhibition by 2,6-dichloro-4-nitrophenol (DCNP) and

pentachlorophenol (PCP). Specification, at page 11. Therefore, one skilled in the art would be able to easily test species belonging to the thermostable phenol sulfotransferase genus for these properties.

Analogously, the genus of glucuronyl transferases encompassed by Applicants' claims all share specific chemical properties and common attributes of being an enzyme capable of conjugating glucuronic acid to a variety of substrates, including nucleophilic substrates, bilirubin, estrogen, or carcinogenic or potentially carcinogenic phenolics, polyaromatic hydrocarbons, and aromatic amines. For example, the specification describes UDP-glucuronyl transferases with the ability to catalyze substrates, such as p-nitrophenol or 2-naphthol, or pro-MII. Specification, at page 41. Therefore, Applicants have provided several properties by which to identify a glucuronyl transferase for use with the present invention. Therefore, one skilled in the art would be able to easily test species belonging to the glucuronyl transferase genus for these chemical properties, the ability to catalyze the conjugation of glucuronic acid.

Furthermore, Applicants have shown that altered levels of the thermostable phenol sulfotransferase and glucuronyl transferase is associated with skatole, and thus a pig's susceptibility to boar taint. Support for this is present in Figures 7-10 and in the specification. In particular, Applicants have shown that the levels of skatole in fat were negatively correlated with the levels of CYP2E1, metabolite F-1, sulfation of pro-MII, and positively correlated with the ratio of pro-MII glucuronidation:sulfation (Table 4). See also in the specification, page 38. Applicants have also shown that the sulfation activity is higher in pigs with low skatole levels in the fat and it is negatively correlated with fat skatole levels in Trial II. Specification, at page 40. A discussion of Trial II is disclosed on pages 36-42 in the specification. Additionally, Applicants have shown that glucuronidation positively correlates with fat

skatole levels. Specification, at page 41. Therefore, any species in these genres which may affect skatole metabolism would likely be associated with susceptibility to boar taint.

The invention claims the detection of the levels of a thermostable phenol sulfotransferase and glucuronyl transferase. The claim recites the genus of thermostable phenol sulfotransferase and glucuronyl transferase. Species belonging to this genus may be identified by chemical properties which are common to all members of the thermostable phenol sulfotransferase genus (the ability to catalyze the sulfate conjugation of micromolar levels of p-nitrophenol and other simple phenols and to be inhibited by 2,6-dichloro-4-nitrophenol (DCNP) and pentachlorophenol (PCP)) and members of the glucuronyl transferase genus (the ability to catalyze the conjugation of glucuronic acid).

These properties would enable one skilled in the art to identify thermostable phenol sulfotransferases and glucuronyl transferases for use in the current method and clearly satisfy the written description requirement.

While the level of every species of the thermostable phenol sulfotransferase genus or glucuronyl transferases may not be associated with susceptibility to boar taint, this does not negate written description as there is ample description of how to identify thermostable phenol sulfotransferases and glucuronyl transferases, how to assay for their level and activity in pigs, and evaluate the data's statistical relevance to developing boar taint.

Applicants clearly have possession of and disclose the identifying characteristics of the genus of thermostable phenol sulfotransferases and glucuronyl transferases. Applicants have thus shown that they were in possession of a method of detecting male pigs susceptible to developing boar taint by detecting protein levels of thermostable phenol sulfotransferases.

For the above-stated reasons, the Applicants have demonstrated that the invention was described such that a person skilled in the art would recognize that the Applicants were in possession of the invention at the time the Application was filed. Therefore, Applicants respectfully request that the Examiner's rejection under 35 U.S.C. § 112, first paragraph be withdrawn and reconsidered.

V. CLAIM REJECTION - 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-6 were rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for the methods as encompassed by claims 1-6. The Examiner states that claims 1-6 while being enabling for a method for determining the susceptibility of a male pig to developing boar taint comprising: a) obtaining liver sample from a male pig and b) immunologically detecting the level of CYP2E1, detecting the rate of glucuronidation of para-nitrophenol or 2-naphthol, or detecting the rate of sulfation of 2-naphthol wherein a high level of CYP2E1, a low rate of glucuronidation of para-nitrophenol or 2-naphthol, or a high rate of sulfation of 2-naphthol as compared to a female control pig or a male control pig or a group of male control pigs indicates that the male pig has a reduced susceptibility to developing boar taint. The Examiner states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants disagree, but in order to execute prosecution, Applicants have amended claim 1 so that it now recites "a method for determining the susceptibility of a male pig to developing boar taint comprising: (a) obtaining a sample from the male pig; and (b) detecting the levels of one or more enzymes selected from the group consisting of (i) CYP2E1; (ii) a

thermostable phenol sulfotransferase that uses 2-naphthol as a substrate and (iii) a glucuronyl transferase that uses para-nitrophenol or 2-naphthol as a substrate, wherein high levels of CYP2E1 and/or high levels of a thermostable phenol sulfotransferase and/or low levels of a glucuronyl transferase indicates that the male pig has a reduced susceptibility to developing boar taint."

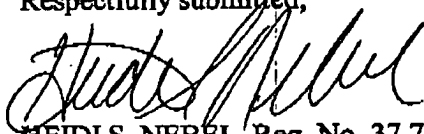
Therefore, Applicants respectfully request that the rejection to claims 1-6 be withdrawn and reconsidered.

VI. CONCLUSION

No fees or extensions of time are believed to be due in connection with this response; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration is respectfully requested.

Respectfully submitted,



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